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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/821,694	03/28/2001	William Daniel Hillis	0450-0001	9199

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EXAMINER

LU, FRANK WEI MIN

ART UNIT PAPER NUMBER

1634

DATE MAILED: 12/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/821,694

Applicant(s)

HILLIS, WILLIAM DANIEL

Examiner

Frank W Lu

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 August 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,6-24,27-31,33-39 and 116-118 is/are pending in the application.
- 4a) Of the above claim(s) 16,17 and 33-35 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,6-15,18-24,27-31,36-39 and 116-118 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 28 March 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on August 9, 2004 has been entered. The claims pending in this application are claims 1, 6-24, 27-31, 33-39, and 116-118 with claims 16, 17, and 33-35 withdrawn from consideration as the result of species election. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the amendment filed on August 9, 2004. Claims 1, 6-15, 18-24, 27-31, 36-39, and 116-118 will be examined.

Claim Objections

2. Claim 29 is objected to because of the following informality: "target target sequence segments" should be "target sequence segments".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 6-15, 18-24, 27-31, 36-39, and 116-118 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

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convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To the extent that the claimed composition/or methods are not described in the instant disclosure, claims 1, 6-15, 18-24, 27-31, 36-39, and 116-118 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

The recitation "at least two oligonucleotide probes that are identical to each other except for a single variable position" is added to the newly amended independent claim 1. Although the specification describes that at least two oligonucleotide probes can be partially overlapping bases (see the specification, page 24, lines 10 and 11 and page 25, last paragraph), the specification fails to define or provide any disclosure to support such claim recitation. Furthermore, there is no support for such claim recitation in the specification at page 24, line 10 to page 26, line 9 as applicant suggests (see applicant's remarks, page 7, third paragraph).

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application."

5. Claims 1, 6-15, 18-24, 27-31, 36-39, 117, and 118 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for performing the method recited in

claims 1, 6-15, 18-24, 27-31, 36-39, 117, and 118 using oligonucleotide probes with specific degenerate nucleotide such as dP or 8-oxo-dG in the variable position, does not reasonably provide enablement for performing the method recited in claims 1, 6-15, 18-24, 27-31, 36-39, 117, and 118 using oligonucleotide probes with a regular degenerate nucleotide in the variable position. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court considered the issue of enablement in molecular biology. The Court summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims. The Court also stated that although the level of skill in molecular biology is high, results of experiments in molecular biology are unpredictable.

To begin, there is no direction or guidance to performing the method recited in claims 1, 6-15, 18-24, 27-31, 36-39, 117, and 118 using oligonucleotide probes with a regular degenerate nucleotide in the variable position. While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no predictability whether the method recite in claim 1, 6-15, 18-24, 27-31, 36-39, 117, and 118 can be performed using oligonucleotide probes with a regular degenerate nucleotide in the variable position.

Claims 1, 6-15, 18-24, 27-31, 36-39, 117, and 118 are directly to a method of employing oligonucleotide probes to obtain information on a position of interest on a target sequence segment of a target nucleic acid analyte. The specification only describes dP, which can approximately equally bind to dT and dC (see the specification, page 21, last paragraph), and 8-oxo-dG, which can pair with C or A (see the specification, page 22, last paragraph). Therefore, at least two oligonucleotides with dP or oxo-dG in the variable position can meet the limitation “wherein hybridization of one or all of the at least two oligonucleotide probes to the target sequence segment occurs only if the degenerately base pairing nucleotide analog or the non-degenerately base pairing nucleotide at the variable position base pairs with a complementary nucleotide at the position of interest, and further wherein none of the at least two oligonucleotide probes hybridizes to the target nucleic acid analyte if there is a mismatch between the degenerately base pairing nucleotide analog or the non-degenerately base pairing nucleotide at the variable position and a nucleotide at the position of interest on the target sequence segment” as recited in claim 18. Since it is known that a regular degenerate base can pair with four different bases (A or T or G or C), at least two oligonucleotides with a regular degenerate base in the variable position cannot meet the limitation “wherein hybridization of one or all of the at least two oligonucleotide probes to the target sequence segment occurs only if the degenerately base pairing nucleotide analog or the non-degenerately base pairing nucleotide at the variable position base pairs with a complementary nucleotide at the position of interest, and further wherein none of the at least two oligonucleotide probes hybridizes to the target nucleic acid analyte if there is a mismatch between the degenerately base pairing nucleotide analog or the non-degenerately base pairing nucleotide at the variable position and a nucleotide at the position

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of interest on the target sequence segment” as recited in claim 18 because a regular degenerate base can not form a mismatch with four different bases (A or T or G or C). Furthermore, the specification does not provide a guidance for performing the method recited in claims 1, 6-15, 18-24, 27-31, 36-39, 117, and 118 using oligonucleotide probes with a regular degenerate nucleotide in the variable position. It will be unpredictable to perform the method recited in claims 1, 6-15, 18-24, 27-31, 36-39, 117, and 118 using oligonucleotide probes with a regular degenerate nucleotide in the variable position.

With these unpredictable factors, the skilled artisan will have no way to predict the experimental results. Accordingly, it is concluded that undue experimentation is required to make the invention as it is claimed. These undue experimentation at least includes to perform the method recited in claims 1, 6-15, 18-24, 27-31, 36-39, 117, and 118 using oligonucleotide probes with a regular degenerate nucleotide in the variable position.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 10-13 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 10 recites the limitation “the target sequence segments hybridized to the array of oligonucleotide probes” in the claim. There is insufficient antecedent basis for this limitation in the claim since there is no hybridization of the target sequence segments to the array of oligonucleotide probes in claim 1. Please clarify.

9. Claim 27 recites the limitation "target nucleic acid analyte is sequenced by analysis of hybridization data obtained from the target sequence segments attached to a substrate surface" in the claim. There is insufficient antecedent basis for this limitation in the claim since there is no the target sequence segments attached to a substrate surface in claim 1. Please clarify.

Response to Arguments

10. Applicant's arguments with respect to claims 1, 6-15, 18-24, 27-31, 36-39, and 116-118 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

12. No claim is allowed.

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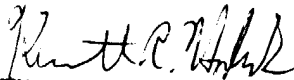
13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (703)872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W Gary Jones, can be reached on (571)272-0745.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
December 3, 2004


KENNETH R. HORLICK, PH.D.
PRIMARY EXAMINER

12/13/04